

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 December 2003 (04.12.2003)

PCT

(10) International Publication Number  
**WO 03/099334 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 47/10**,  
47/14, 47/06, 47/32, 47/44, 31/44

(81) Designated States (*national*): AE, AL, AU, BA, BR, CA,  
CN, CO, CU, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT,  
LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, US, VN,  
YU, ZA, ZW.

(21) International Application Number: PCT/EP03/05524

(22) International Filing Date: 27 May 2003 (27.05.2003)

(84) Designated States (*regional*): Eurasian patent (AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,  
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

(25) Filing Language: English

(26) Publication Language: English

**Declarations under Rule 4.17:**

**(30) Priority Data:**

02011830.3	28 May 2002 (28.05.2002)	EP
102 23 828.6	28 May 2002 (28.05.2002)	DE
103 11 613.3	14 March 2003 (14.03.2003)	DE

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, ID,  
IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL,  
SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,  
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)

(71) Applicant (*for all designated States except US*): **ALTANA  
PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Kon-  
stanz (DE).

— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for all designations  
— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for all designations  
— of inventorship (Rule 4.17(iv)) for US only

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BOLLE, Christina**  
[DE/DE]; Bahnhofstr. 54, 55278 Hahnheim (DE). **LIN-  
DER, Rudolf** [AT/DE]; Lindauerstr. 40, 78464 Konstanz  
(DE).

**Published:**

— with international search report

(74) Common Representative: **ALTANA PHARMA AG**;  
Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: TOPICALLY APPLICABLE PHARMACEUTICAL PREPARATION

(57) Abstract: A topical pharmaceutical preparation for administering a slightly soluble PDE4 inhibitor is described. A surprisingly good systemic bioavailability is observed with this dosage form.

WO 03/099334 A1

## Topically applicable pharmaceutical preparation

### Technical field

The present invention relates to the field of pharmaceutical technology and describes a topically applicable pharmaceutical preparation comprising as active ingredient a slightly soluble PDE 4 inhibitor. The invention additionally relates to processes for producing the topically applicable pharmaceutical preparation and to the use for the treatment of disorders of the skin, of the eyes and of the airways.

### Prior art

Cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are currently of special interest as a new generation of active ingredients for treating inflammatory disorders, especially disorders of the airways such as asthma or airway obstructions (such as, for example, COPD = chronic obstructive pulmonary disease). A number of PDE 4 inhibitors are currently undergoing advanced clinical testing, including a dosage form for oral administration comprising the active ingredient N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast). This and other compounds with a benzamide structure and their use as cyclic nucleotide phosphodiesterase (PDE) inhibitors are described in WO 95/01338. These active ingredients are proposed in WO 95/01338 also for the treatment of certain disorders of the skin (such as, for example, dermatoses). WO 00/53182 proposes the use of roflumilast or its N-oxide for the treatment of multiple sclerosis.

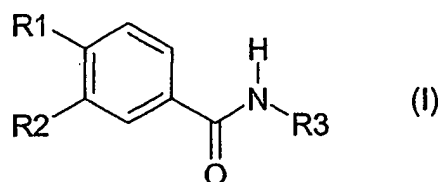
For treating disorders of the skin it is desirable to provide the active pharmaceutical ingredient in a pharmaceutical preparation suitable for topical application. As the skilled person is aware, however, the provision of dosage forms for topical application may prove to be extremely difficult or is impossible if the intention is to administer an active ingredient which has a very low solubility. Thus, for example, the solubility in water found for the PDE 4 inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast), which is described in WO 95/01338, is only 0.53 mg/l at 21°C.

### Description of the invention

It has now been found, surprisingly, that topically applicable pharmaceutical preparations comprising the slightly soluble PDE 4 inhibitor roflumilast show a very good effect in the treatment of dermatoses on local, dermal application. Also found, entirely surprisingly, besides the local effect, is an excellent systemic effect which is comparable with that of an oral dosage form.

A first aspect of the invention is therefore a pharmaceutical preparation which can be administered topically and comprises an active pharmaceutical ingredient together with one or more pharmaceutical carriers and/or excipients suitable for topical administration, the active pharmaceutical ingredient being a compound selected from the group consisting of roflumilast, salts of roflumilast, the N-oxide of roflumilast and salts thereof.

Roflumilast is the INN for a compound of the formula I



in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl.

This compound has the chemical name N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast). The N-oxide of roflumilast has the chemical name 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl 1-oxide)benzamide.

This compound of the formula I, its salts, the N-oxide, its salts and the use of these compounds as phosphodiesterase (PDE) 4 inhibitors are described in the international patent application WO 95/01338.

Salts suitable for compounds of the formula I - depending on the substitution - are all acid addition salts but, in particular, all salts with bases. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids and bases normally used in pharmaceutical technology. Pharmacologically unacceptable salts which, for example, may be the initial products of the process for preparing the compounds of the invention on the industrial scale are converted into pharmacologically acceptable salts by processes known to the skilled worker. Those suitable on the one hand are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid, or 3-hydroxy-2-naphthoic acid, the acids

being employed to prepare the salts in the equimolar ratio of amounts, or one differing therefrom - depending on whether the acid is monobasic or polybasic and depending on which salt is desired.

On the other hand, salts with bases are also particularly suitable. Examples of basic salts which may be mentioned are lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, once again the bases being employed to prepare the salts in the equimolar ratio of amounts or one differing therefrom.

The proportion (in per cent by weight based on the weight of the finished pharmaceutical preparation; w/w) of active pharmaceutical ingredient in the pharmaceutical preparation of the invention is usually from 0.001 to 50% by weight. The proportion of active pharmaceutical ingredient is preferably up to 1% by weight.

The pharmaceutical carriers and/or excipients suitable for topical administration are preferably according to the invention conventional carriers and/or excipients known to the skilled person in connection with pharmaceutical preparations for dermal administration (= dermatologicals). Examples which may be mentioned are carriers and/or excipients which are suitable for producing dusting powders, emulsions, suspensions, sprays, oils, ointments, greasy ointments, creams, pastes, gels, foams or solutions, and transdermal therapeutic systems.

The topical pharmaceutical preparation of the invention can be produced by processes familiar to the skilled person.

Conventional dermatologicals and their production, and preferred carriers and/or excipients for the individual pharmaceutical preparations are described, for example, in the textbook "Pharmazeutische Technologie" (Sucker, Fuchs, Speiser, Georg Thieme Verlag, 1978 from page 629).

In a first embodiment of the invention, the topical pharmaceutical preparation of the invention is a semi-solid dosage form. Examples which may be mentioned are, in particular, ointments (e.g. solution ointment, suspension ointment), creams, gels or pastes.

Oil-in-water or water-in-oil emulsions are normally referred to as creams. Chiefly used for the oily phase are fatty alcohols, e.g. lauryl, cetyl or stearyl alcohol, fatty acids, e.g. palmitic or stearic acid, liquid or solid paraffins or ozokerite, liquid to solid waxes, e.g. isopropyl myristate, natural or partially synthetic fat, e.g. coconut fatty acid triglyceride, hardened oils, e.g. hydrogenated peanut or castor oil, or fatty acid partial esters of glycerol, e.g. glycerol monostearate or glycerol distearate. Suitable emulsifiers are surface-active substances, e.g. nonionic surfactants, e.g. fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglycerol fatty acid esters or polyoxyethylene sorbitan fatty acid es-

ters (Tween®: ICI,) sorbitan fatty acid esters (Span®: ICI), such as, for example, sorbitan oleate and/or sorbitan isostearate, sterols, also polyoxyethylene fatty alcohol ethers or fatty acid esters, or anionic surfactants such as alkali metal salts of fatty alcohol sulphates, e.g. sodium lauryl sulphate, sodium cetyl sulphate or sodium stearyl sulphate, which are normally used in the presence of said fatty alcohols, e.g. cetyl alcohol or stearyl alcohol. It is possible to add to the aqueous phase *inter alia* agents which prevent the cream drying out, e.g. polyalcohols such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, also preservatives, fragrances etc.

Ointments may be anhydrous and contain as base the paraffins which are suitable for topical use and are liquid at body temperature, especially low-viscosity paraffin, also the said natural or partially synthetic fats, e.g. coconut fatty acid triglyceride, hardened oils, e.g. hydrogenated peanut or castor oil, fatty acid partial esters of glycerol, e.g. glycerol monostearate and distearate, silicones, e.g. polydimethylsiloxanes, e.g. hexamethyldisiloxane or octamethyltrisiloxane, and, for example, the fatty alcohols mentioned in connection with the hydrous creams and increasing the water uptake capacity, and sterols, wool waxes, other emulsifiers and/or other additives.

In the case of gels, a distinction is made between hydrous, anhydrous and low water-content gels, which consist of swellable, gel-forming material. Chiefly suitable are transparent hydrogels based on inorganic or organic macromolecules. Macromolecular inorganic components with gel-forming properties are predominantly hydrous or water-absorbing silicates such as aluminium silicates, e.g. bentonite, magnesium-aluminium silicates, e.g. Veegum® - Vanderbilt Exp. Corp., or colloidal silica, e.g. Aerosil® - Degussa. Examples of macromolecular organic substances used are natural, semisynthetic or synthetic polymers. Natural and semisynthetic polymers are derived, for example, from polysaccharides with different carbohydrate units, such as cellulose, starch, tragacanth, gum arabic, agar-agar, gelatin, alginic acid and salts thereof, e.g. sodium alginate and derivatives thereof, lower alkylcellulose, for example methyl- or ethylcellulose, carboxy- or hydroxy-lower-alkylcellulose, e.g. carboxymethyl- or hydroxypropylcellulose. The units of synthetic, gel-forming polymers are, for example, unsaturated, substituted aliphatic compounds such as vinyl alcohol, vinylpyrrolidone, acrylic or methacrylic acid. Examples to be mentioned of such polymers are polyvinyl alcohol derivatives such as Polyviol® - Wacker, polyvinylpyrrolidones, such as Kollidon® - BASF or Polyplasdon® - General Aniline, polyacrylates and polymethacrylates, such as Rohagit S® - Rohm und Haas. It is possible to add conventional additives such as preservatives or fragrances to the gels.

Pastes are creams or ointments with the constituents mentioned hereinbefore and secretion-absorbing dusting powder constituents such as metal oxides, e.g. titanium oxide or zinc oxide, also talc and/or aluminium silicates, which have the task of binding moisture or secretions.

In a preferred embodiment of the invention, the topical pharmaceutical preparation of the invention is a

semisolid pharmaceutical preparation, with one of the excipients being polyethylene glycol, in particular polyethylene glycol 400.

In a further embodiment of the invention, the topical pharmaceutical preparation of the invention is a transdermal therapeutic system (TTS), for example a system as described in *Pharmazeutische Technologie: Moderne Arzneiformen*, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart 1997, pages 81 et seq. TTSs are characterized in principle by a defined supply of medicinal substance to the skin, a total dose of the medicinal substance in the TTS, a total area and an area which is possibly different therefrom for release of the medicinal substance, a covering sheet (backing layer) which is impermeable to the medicinal substance, a medicinal substance reservoir, a control element which controls the supply of medicinal substance to the skin, a (pressure-sensitive) adhesive layer and a detachable protective layer. It is possible on occasions for more than one function to be fulfilled by one and the same element, e.g. reservoir, control and adhesive functions by a suitable adhesive matrix. From the viewpoint of pharmaceutical technology, TTSs are categorized according to the way the control function is achieved, that is to say how it controls the supply of medicinal substance to the skin. Examples which are mentioned here are TTSs with membrane permeation-controlled release (membrane moderated drug delivery), TTSs with matrix diffusion-controlled release and TTSs with microreservoir solution-controlled release.

TTSs with membrane permeation-controlled release are characterized by a polymer membrane composed of a PVA-VA copolymer (Chronomer®) which controls the permeation of the medicinal substance from the reservoir into the skin. The medicinal substance is initially in the form of solid particles or as a dispersion or solution in the reservoir. The polymer membrane can be attached to the reservoir in various ways (extrusion, encapsulation, microencapsulation). TTSs with matrix diffusion-controlled release have a comparatively simpler structure. They contain no separate control element. The release of medicinal substance is controlled by a lipophilic or hydrophilic polymer matrix and/or the adhesive layer. It is possible to distinguish, according to the characteristics of the matrix, between TTSs with a matrix in gel form and TTSs which represent solid polymer laminates. The medicinal substance reservoir is formed by the medicinal substance dissolved in the matrix (monolithic system) or a homogeneous dispersion of solid medicinal substance particles. A matrix TTS can be produced by mixing the medicinal substance particles with a viscous liquid or semisolid polymer at room temperature, followed by crosslinking the polymer chains. A further possibility is also to mix the medicinal substance at elevated temperature with softened polymer (hot melt technique), or the two components (dissolved in an organic solvent) are mixed together and the solvent is then removed in vacuo (solvent evaporation). Shaping is possible by pouring into suitable moulds, spreading with special devices (knives) or by extrusion. In the case of TTSs with microreservoir solution-controlled release (microsealed drug delivery, MDD principle), numerous microcompartments containing the active ingredient and 10-200 µm in size are embedded in a matrix which represents both reservoir and delivery-control element. Because of the

matrix, these TTSs are actually assigned to the matrix systems. For production, the medicinal substance is initially dispersed together with water and 40% polyethylene glycol 400 in isopropyl palmitate, which acts as permeation promoter. The resulting dispersion is incorporated by using a special high-energy dispersion technique into a viscous silicone elastomer which simultaneously undergoes catalytic polymerization. The medicinal substance-containing matrix can be shaped specifically by melt or extrusion techniques before it is combined with the carrier in the manner already described. Depending on the physicochemical properties of the medicinal substances and the intended liberation, it is possible to cover the matrix with a layer of a biocompatible polymer in order thus to modify the mechanism and the rate of liberation.

In another embodiment of the invention, the topical pharmaceutical preparation of the invention is a dosage form for use on the eye (ophthalmologicals). Examples which may be mentioned in this connection are eyebaths or eye lotions, eye inserts, eye ointments, eye sprays, eye drops, preparations for intraocular injection and eyelid ointments. In a preferred embodiment, the dosage form of the invention is an eye ointment or eye drops. Eye drops preferably comprise according to the invention aqueous or oily suspensions of the active ingredient. It is preferred in this connection for the particle size of the active ingredient employed to be 90% less than 10  $\mu\text{m}$ .

Preferably used in the case of aqueous suspensions are suspension stabilizers such as, for example, substituted celluloses (e.g. methylcellulose, hydroxypropylmethylcellulose), polyvinyl alcohol, polyvinylpyrrolidone, in addition to preservatives (e.g. chlorocresol, phenylmercury compounds, phenylethanol, benzalkonium chloride or mixtures of individual components) and, where appropriate, sodium chloride to adjust to isotonicity. Preferably employed according to the invention in the case of oily eye drops are castor oil, peanut oil or medium chain length triglycerides. It is possible in the case of eye ointments to use according to the invention ointment bases which have the following properties: sterility or extremely low microbe content, non-irritating, good activity, good distribution of the active ingredient or its solution in the ointment, suppleness, rapid dispersion as fine film over the eyeball, good adhesion to the eye, good stability and low impairment of vision. Hydrocarbon- or cholesterol-containing bases will therefore preferably be employed according to the invention for eye ointments. In the case of petrolatum, liquid paraffin is preferably added for consistency reasons. To achieve good spreading, it is preferred according to the invention to provide compositions of limited viscosity. The viscosity at 32°C is preferably below 1 000 mPa.s, and the yield point is preferably below 300 mPa. In the case of suspension ointments it is preferred according to the invention for 90% of the active ingredient particles to be below 10  $\mu\text{m}$ , and no particles above 90  $\mu\text{m}$  should occur. In the case of water/oil emulsion ointments, it is preferred according to the invention to add preservatives such as benzalkonium chloride, thiomersal or phenylethyl alcohol.

**Examples****Production of the dosage forms of the invention****Example 1**

550 grams contain

Polyethylene glycol 400	440.00 g
Carbopol 934®	8.25 g
Roflumilast	1.375 g
Sodium hydroxide solution	q.s.
Purified water	to 550.00 g

Production takes place by dissolving the active ingredient in the stated amount of polyethylene glycol at about 60-70°C. About 90 grams of purified water are added and mixed homogeneously, and the Carbopol 934 is homogeneously dispersed therein with a high-speed stirrer. While stirring slowly, sodium hydroxide solution is added until a pH of 6.5-7.5 is reached. The remaining water is added up to the final weight and homogeneously mixed.

**Example 2**

550 grams contain

Roflumilast	1.65 g
Polyethylene glycol 400	440.00 g
Polyethylene glycol 4000	to 550.0 g

Production takes place by treating the two polyethylene glycols to 70°C to give a clear melt. The active ingredient is added likewise to give a clear solution. The preparation is cooled to room temperature while stirring slowly.

**Example 3**

550 grams contain

Roflumilast	1.10 g
Tego Care 150® (Th. Goldschmidt)	27.50 g
Neutral oil (Miglyol 812®)	137.50 g



Polyethylene glycol 400	275.00 g
Cetostearyl alcohol	11.00 g
Purified water	to 550 g

Production takes place by making a clear solution of the neutral oil, the cetostearyl alcohol and Tego Care 150 at about 70°C. The polyethylene glycol, in which the roflumilast has been dissolved, is likewise stirred in using a high-speed stirrer. The water heated to 70°C is added to the lipid phase. A Tur-rax is used for homogenization. The preparation is then stirred until cold (room temperature).

#### **Example 4**

100 grams contain

Roflumilast	0.25 g
Neutral oil (Miglyol 812®)	16.00 g
Glycerol monostearate	8.00 g
Cremophor A6® (BASF)	4.00 g
Polyethylene glycol 400	62.50 g
Purified water	to 100.00 g

Production takes place by heating all the components (apart from water) together to about 70-80°C to give a clear solution. The water is then added while stirring, and the preparation produced in this way is cooled to room temperature while stirring.

#### **Example 5**

100 grams contain

Roflumilast	0.25 g
Liquid paraffin	15.00 g
Wool wax	5.00 g
White petrolatum	to 100 g

Production takes place by making a clear melt of the liquid paraffin, the wool wax and the white petrolatum at about 80°C. The micronized active ingredient is added, and the preparation is stirred until it has cooled to room temperature.

**Example 6**

Roflumilast	0.10 g
Liquid paraffin	10.00 g
Wool wax	5.00 g
White petrolatum	to 100 g

Production takes place in analogy to Example 5.

**Example 7**

Roflumilast	0.10 g
Neutral oil (Miglyol 812®)	16.00 g
Glycerol monostearate	8.00 g
Cremophor A6® (BASF)	2.00 g
Polyethylene glycol 400	62.50 g
Purified water	to 100.00 g

Production takes place in analogy to Example 4.

**Example 8**

Roflumilast	0.10 g
Neutral oil ( Miglyol 812®)	16.00 g
Glycerol monostearate	8.00 g
Cremophor A6® (BASF)	4.00 g
Polyethylene glycol 400	62.50 g
Purified water	to 100.00 g

Production takes place in analogy to Example 4.

**Example 9**

Composition of an eye ointment (quantity for 1 000 grams)

Roflumilast	1 g
Cetyl alcohol	4 g
High-viscosity paraffin	200 g
White petrolatum	795 g

Production: A clear melt of the cetyl alcohol, the high-viscosity paraffin and the white petrolatum is prepared at about 70°C. The micronized roflumilast (90% of the particles below 10  $\mu\text{m}$ ) is stirred in, and a homogeneous dispersion is prepared using an Ultra-Turrax. The suspension is cooled to room temperature while stirring and used to fill suitable tubes.

#### Example 10

Composition of a drop solution in the form of an emulsion (quantity for 1 000 millilitres)

Roflumilast	1.5 g
Medium chain length triglycerides	100.0 g
Lecithin	12.0 g
Glycerol	25.0 g
Thiomersal	0.1 g
Purified water	to 1 000 ml

Production: First the roflumilast and then the lecithin are dissolved in the medium chain length triglycerides and the glycerol at 30°C-40°C. While stirring vigorously, the purified water is added and then homogenized until the droplet size of the disperse phase is below 500 nm. The thiomersal is dissolved by stirring. The emulsion is filtered through a 0.45  $\mu\text{m}$  filter and dispensed into suitable containers.

#### Example 11

Composition of a nose ointment (quantity for 1 000 grams)

Roflumilast	1 g
Cetyl alcohol	4 g
Wool wax	50 g
High-viscosity paraffin	200 g
White petrolatum	745 g

Production: A clear melt of the cetyl alcohol, the high-viscosity paraffin, the wool wax and the white petrolatum is prepared at about 70°C. The micronized roflumilast (90% of the particles below 10  $\mu\text{m}$ ) is stirred in, and a homogeneous dispersion is prepared using an Ultra-Turrax. The suspension is cooled to room temperature while stirring and used to fill suitable tubes.

## Investigations of the pharmacokinetics of the topical pharmaceutical preparations

### Comparison of pharmacokinetics parameters of topical pharmaceutical preparations of the invention with oral form

#### Example A

A preparation corresponding to Example 7 and a preparation corresponding to Example 8 containing [ $^{14}\text{C}$ ]roflumilast were applied to shaven areas of rat skin (5 male Wistar rats) 4 cm<sup>2</sup> in size. The radioactivity concentrations were measured in the plasma after 1 h, 4 h, 8 h, 24 h and in the urine (0-24 h) (n = 5). The dose was 1.7 mg/kg.

#### Results:

Preparation of Example 7: C<sub>max</sub>: 0.214 mg equiv./l, AUC(0-24 h): 4.13 (mg equiv./l × h)

Preparation of Example 8: C<sub>max</sub>: 0.214 mg equiv./l, AUC(0-24 h): 3.99 (mg equiv./l × h)

The results standardized to 1 mg/kg are

Preparation of Example 7: C<sub>max</sub>: 0.126, AUC: 2.43

Preparation of Example 8: C<sub>max</sub>: 0.126, AUC: 2.35

Comparison with kinetic parameters after oral administration of 1 mg/kg:

C<sub>max</sub>: 0.225 mg equiv./l, AUC(0-24 h): 3.10 (mg equiv./l × h)

The ratio of the AUC (preparation of Example 7) to the AUC (oral) is 78% and that of the AUC (preparation of Example 8) to the AUC (oral) is 76%.

Results of comparison of the excretions with the urine:

Preparation of Example 7: 19.4% of the dose

Preparation of Example 8: 18.0% of the dose

Oral administration: 18.4% of the dose

#### Conclusion:

After percutaneous administration of 1.7 mg/kg [ $^{14}\text{C}$ ]roflumilast to rats, the total radioactivity is transported well through the skin and reaches a maximum plasma level of 0.214 mg equiv./l after 4 h, irrespective of the preparation employed. Based on the total radioactivity, the AUCs and the excretions with the urine after percutaneous administration are negligibly different from those after oral administration.

**Example B**

A preparation corresponding to Example 5 containing [ $^{14}\text{C}$ ]roflumilast was applied to a shaven area of rat skin (male Wistar rat) 4 cm<sup>2</sup> in size. The radioactivity concentrations were measured in the plasma after 1 h, 4 h, 8 h, 24 h and in the urine (0-24 h) (n = 5). The dose was 1.77 mg/kg.

Preparation of Example 5: C<sub>max</sub>: 0.331 mg equiv./l, AUC(0-24 h): 4.99 (mg equiv./l × h)

The results standardized to 1 mg/kg are

Preparation of Example 5: C<sub>max</sub>: 0.187, AUC: 2.82

Comparison with kinetic parameters after oral administration of 1 mg/kg:

C<sub>max</sub>: 0.225 mg equiv./l, AUC(0-24 h): 3.10 (mg equiv./l × h)

Results of comparison of the excretions with the urine:

Preparation of Example 5: 22.0% of the dose

Oral administration: 18.4% of the dose

**Conclusion:**

These data show that roflumilast is absorbed from the preparation of Example 5 even somewhat better than from the preparations corresponding to Example 7 or 8. The excretion with the urine in the 24 h after administration is 22%, which is also in the region of the excretion with the urine after dermal administration of the preparations corresponding to Example 7 or 8. Comparison with oral administration shows that, irrespective of the composition of the topical preparation, similar C<sub>max</sub> and AUCs and similar excretions with the urine are achieved.

**Industrial applicability**

The dosage forms of the invention can be employed for the treatment and prevention of all diseases regarded as treatable or preventable through the use of PDE 4 inhibitors. Selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are suitable on the one hand as bronchial therapeutic agents (for the treatment of airway obstructions owing to their dilating effect but also owing to their effect increasing the respiratory rate and respiratory drive) and for eliminating erectile dysfunction owing to the vasodilating effect, but on the other hand especially for the treatment of disorders, especially of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the central nervous system, of the intestine, of the eyes and of the joints, which are promoted by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. The pharmaceutical preparations of the invention can therefore be used in human and veterinary medicine for example for the treatment and prophylaxis of the following diseases: acute and chronic (especially inflammatory and allergen-induced) airway disorders of various aetiologies (bronchitis, allergic bronchitis, bronchial asthma, COPD); dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders based on excessive release of TNF and leukotrienes, e.g. disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states), disorders of the immune system (AIDS, multiple sclerosis), types of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)] and generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders based on allergic and/or chronic abnormal immunological reactions in the region of the upper airways (pharyngeal space, nose) and adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis, conjunctivitis caused by bacteria, viruses or fungi, inflammatory states after intraocular lens implantation, inflammation of the optic nerve (neuritis nervi optici), keratitis, dry eye syndrome (keratitis sicca), uveitis, glaucoma, retinal oedema, retinitis pigmentosa, diabetic retinopathy, and nasal polyps; but also cardiac disorders which can be treated by PDE inhibitors, such as, for example, heart failure, or disorders which can be treated owing to the tissue-relaxant effect of PDE inhibitors, such as, for example, erectile dysfunction or colic of the kidneys and ureters connected with kidney stones; or else disorders of the CNS such as, for example, depressions or arteriosclerotic dementia.

The pharmaceutical preparations of the invention are particularly suitable for the treatment of disorders of the skin such as dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars,

discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders. Mention may preferably be made of the use of the pharmaceutical preparations of the invention in the treatment of psoriasis and atopic eczema.

The invention therefore also relates further to the use of roflumilast, salts of roflumilast, the N-oxide of roflumilast or salts thereof for producing a topical pharmaceutical preparation for dermal administration for the treatment of disorders of the skin which are regarded as treatable or preventable by application of PDE 4 inhibitors. Mention may preferably be made in this connection of dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders.

The invention further relates to a method for the treatment of mammals, including humans, suffering from one of the abovementioned diseases. The method is characterized in that a therapeutically effective and pharmacologically suitable amount of an active pharmaceutical ingredient selected from the group of compounds roflumilast, salts of roflumilast, the N-oxide of roflumilast and salts thereof is administered to the mammal with the disease, with the active pharmaceutical ingredient being administered in a topical pharmaceutical preparation of the invention. The disease is preferably a disorder of the skin such as dermatoses (especially of a proliferative, inflammatory and allergic nature) such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, lichen simplex, sunburn, pruritus in the genitoanal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders. The method is characterized in that the administration takes place by dermal administration, i.e. through application of the topical pharmaceutical preparations of the invention to the skin or mucous membranes.

In another preferred embodiment, the invention relates to the treatment of mammals, including humans, suffering from an eye disorder which is regarded as treatable or preventable through the use of PDE4 inhibitors. This eye disorder is preferably selected from the group of allergic conjunctivitis, conjunctivitis caused by bacteria, viruses or fungi, inflammatory states after intraocular lens implantation, inflammation of the optic nerve (neuritis nervi optici), keratitis, dry eye syndrome (keratitis sicca), uveitis, glaucoma, retinal oedema, retinitis pigmentosa and diabetic retinopathy. The eye disorder is preferably allergic conjunctivitis, conjunctivitis caused by bacteria, viruses or fungi, inflammatory states after intraocular lens implantation or uveitis. The method is characterized in that the administration takes place by application of the preparation of the invention to the eye.

The good systemic availability surprisingly observed on topical administration makes the pharmaceuti-

cal preparations of the invention additionally suitable for systemic treatment and thus for the treatment of all other diseases which are regarded as treatable or preventable through application of PDE 4 inhibitors, especially the abovementioned diseases.

The invention therefore also relates further to the use of roflumilast, salts of roflumilast, the N-oxide of roflumilast or salts thereof for producing a topical pharmaceutical preparation for dermal administration for the systemic treatment of diseases regarded as treatable or preventable by application of PDE 4 inhibitors. Mention may preferably be made in this connection of acute and chronic (especially inflammatory and allergen-induced) airway disorders of various aetiologies (bronchitis, allergic bronchitis, bronchial asthma, COPD), and disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states).

The pharmaceutical preparations of the invention are moreover particularly suitable for administration to groups of patients who are suffering from the abovementioned diseases and have problems in taking pharmaceutical preparations to be administered orally, such as, for example, bedridden patients, patients in intensive medical care, patients with swallowing difficulties and children.

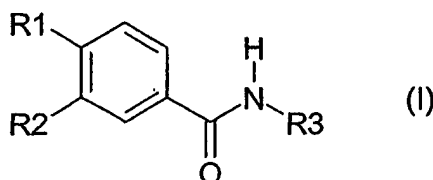
The invention further relates to a method for the treatment of mammals, including humans, suffering from one of the abovementioned diseases. The method is characterized in that a therapeutically effective and pharmacologically suitable amount of an active pharmaceutical ingredient selected from the group of compounds roflumilast, salts of roflumilast, the N-oxide of roflumilast and salts thereof is administered to the mammal with the disease, with the active pharmaceutical ingredient being administered in a topical pharmaceutical preparation of the invention. The disease is preferably acute and chronic (especially inflammatory and allergen-induced) airway disorders of various aetiologies (bronchitis, allergic bronchitis, bronchial asthma, COPD), and disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states). The method is characterized in that administration takes place by dermal administration, i.e. through application of the topical pharmaceutical preparations of the invention to the skin or mucous membranes.

The dosage forms of the invention comprise the active pharmaceutical ingredient in the dose customary for the treatment of the particular disease. The dosage of the active ingredient is of the order of magnitude customary for PDE inhibitors, it being possible to administer the daily dose in one or more dosage units. Customary dosages are disclosed for example in WO 95/01338. The normal dose on systemic therapy (oral) is between 0.001 and 3 mg per kilogram and day. Dosage forms preferred according to the invention for topical administration contain from 0.005 mg to 5 mg of roflumilast, preferably from 0.01 mg to 2.5 mg, particularly preferably 0.1 mg to 0.5 mg of roflumilast per dosage unit. Examples of pharmaceutical preparations of the invention contain 0.01 mg, 0.1 mg, 0.125 mg, 0.25 mg and 0.5 mg of roflumilast per dosage unit.



**Claims**

1. Topically applicable pharmaceutical preparation comprising an active pharmaceutical ingredient together with one or more pharmaceutical carriers and/or excipients suitable for topical administration, where the active pharmaceutical ingredient is a compound selected from the group consisting of roflumilast, salts of roflumilast, the N-oxide of the pyridine residue of roflumilast or salts thereof.
2. Topically applicable pharmaceutical preparation according to Claim 1, where roflumilast is a compound of the formula I



in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl.

3. Topical pharmaceutical preparation according to Claim 1, which is a semisolid dosage form selected from the group of ointments (e.g. solution ointment, suspension ointment), creams, gels or pastes.
4. Topical pharmaceutical preparation according to Claim 1, which is a transdermal therapeutic system (TTS).
5. Use of roflumilast, salts of roflumilast, the N-oxide of roflumilast or salts thereof for producing a topical pharmaceutical preparation for dermal administration for the systemic treatment of diseases regarded as treatable or preventable through use of PDE 4 inhibitors.
6. Use of roflumilast, salts of roflumilast, the N-oxide of roflumilast or salts thereof for producing a topical pharmaceutical preparation for dermal administration for the treatment of disorders of the skin regarded as treatable or preventable through use of PDE 4 inhibitors.
7. Method for treating mammals, including humans, suffering from a dermatosis regarded as treatable or preventable through use of PDE 4 inhibitors, characterized in that a therapeutically effective and pharmacologically suitable amount of an active pharmaceutical ingredient selected from the group of compounds roflumilast, salts of roflumilast, the N-oxide of roflumilast and salts

- thereof is administered to the mammal with the disorder, with the active pharmaceutical ingredient being administered in a topical pharmaceutical preparation of the invention according to Claim 1, and administration taking place by dermal administration.
8. Method according to Claim 7, where the dermatosis is psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, lichen simplex, sunburn, pruritus in the genital-anal region, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and extensive pyodermas, endogenous and exogenous acne, acne rosacea or other proliferative, inflammatory and allergic skin disorders.
  9. Method for treating mammals, including humans, suffering from a disease regarded as treatable or preventable through use of PDE 4 inhibitors, characterized in that a therapeutically effective and pharmacologically suitable amount of an active pharmaceutical ingredient selected from the group of compounds roflumilast, salts of roflumilast, the N-oxide of roflumilast and salts thereof is administered to the mammal with the disorder, with the active pharmaceutical ingredient being administered in a topical pharmaceutical preparation of the invention according to Claim 1, and administration taking place by dermal administration.
  10. Method according to Claim 9, where the disease is acute and chronic (especially inflammatory and allergen-induced) airway disorders of various aetiologies (bronchitis, allergic bronchitis, bronchial asthma, COPD) or disorders of the arthritic type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic states).
  11. Topically applicable pharmaceutical preparation according to Claim 1, characterized in that it is a dosage form for use on the eye.
  12. Topically applicable pharmaceutical preparation according to Claim 11, characterized in that it comprises eye drops.
  13. Topically applicable pharmaceutical preparation according to Claim 11, characterized in that it comprises a suspension of the active pharmaceutical ingredient in the carriers and/or the excipients.
  14. Topically applicable pharmaceutical preparation according to Claim 11, characterized in that it comprises an eye ointment.
  15. Method for treating mammals, including humans, suffering from an eye disorder which is regarded as treatable or preventable through the use of PDE 4 inhibitors, characterized in that a therapeutically effective and pharmacologically suitable amount of an active pharmaceutical ingredient selected from the group of compounds roflumilast, salts of roflumilast, the N-oxide of ro-

flumilast and salts thereof is administered to the mammal with the disorder, with the active pharmaceutical ingredient being administered in the topical pharmaceutical preparation of the invention according to Claim 11.

16. Method according to Claim 15, where the disease is allergic conjunctivitis, conjunctivitis caused by bacteria, viruses or fungi, inflammatory states after intraocular lens implantation, inflammation of the optic nerve (neuritis nervi optici), keratitis, dry eye syndrome (keratitis sicca), uveitis, glaucoma, retinal oedema, retinitis pigmentosa or diabetic retinopathy.
17. Method according to Claim 16, where allergic conjunctivitis, conjunctivitis caused by bacteria, viruses or fungi, inflammatory states after intraocular lens implantation or uveitis is involved.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/05524

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/10 A61K47/14 A61K47/06 A61K47/32 A61K47/44  
A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, WPI Data, BIOSIS, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 01338 A (BYK GULDEN LOMBERG CHEM FAB ; AMSCHLER HERMANN (DE)) 12 January 1995 (1995-01-12)	1-7,9, 11-15
Y	page 15; example 5 page 19, paragraph 2 - page 20, paragraph 5 page 19, paragraphs 1,2 page 21, paragraph 3 - paragraph '0004!	1-17
X	WO 01 32165 A (ZUSSMAN BARRY D ; MURDOCH ROBERT D (GB); SMITHKLINE BEECHAM PLC (GB);) 10 May 2001 (2001-05-10)	1-6,9, 11-15
Y	page 6, line 3 page 6, line 26 - line 31 ----- -/-	1-17

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*B\* document member of the same patent family

Date of the actual completion of the international search

28 July 2003

Date of mailing of the international search report

04/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Giacobbe, S.

## INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 03/05524

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 38155 A (CHANG YUJUN ; MERCK & CO INC (US)) 16 May 2002 (2002-05-16)	1-7,9,15
Y	page 3, line 6 - line 10 page 3, line 26	1-17
X	WO 00 18388 A (ALCON LAB INC ; CAGLE GERALD (US); STROMAN DAVID W (US); YANNI JOHN M) 6 April 2000 (2000-04-06)	1-3,5,6,9,11-15
Y	page 1, line 10 page 2, line 30 - page 3, line 3 page 3, line 27 - line 28 page 3, line 14 - line 18 page 9, line 10	1-17
Y	US 4 753 945 A (GILBARD JEFFREY P ET AL) 28. Juni 1988 (1988-06-28) column 1, line 16 - line 30 column 1, line 62 - line 64 claims 1,6	1-17
Y	US 5 011 843 A (SHELL JOHN W) 30 April 1991 (1991-04-30) column 1, line 14 - line 21 column 1, line 39 - line 41 column 1, line 44 - line 46 column 3, line 49	1-17
Y	US 6 174 878 B1 (YANNI JOHN M ET AL) 16 January 2001 (2001-01-16) column 5, line 16 - line 17 column 6, line 38	1-17
P,Y	REID P: "ROFLUMILAST" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 3, no. 8, August 2002 (2002-08), pages 1165-1170, XP001119630 ISSN: 0967-8298 page 1169; tables 1,4	1-17

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/05524

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 7-10 and 15-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/05524

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9501338	A	12-01-1995	AT 217612 T	15-06-2002
			AU 687087 B2	19-02-1998
			AU 7490794 A	24-01-1995
			CA 2165192 A1	12-01-1995
			CN 1126468 A ,B	10-07-1996
			CZ 9600001 A3	12-06-1996
			DE 59410119 D1	20-06-2002
			DK 706513 T3	09-09-2002
			WO 9501338 A1	12-01-1995
			EP 0706513 A1	17-04-1996
			ES 2176252 T3	01-12-2002
			FI 956333 A	29-12-1995
			HU 73232 A2	29-07-1996
			JP 8512041 T	17-12-1996
			JP 3093271 B2	03-10-2000
			NO 955211 A	21-12-1995
			NZ 271316 A	24-11-1997
			PL 311820 A1	18-03-1996
			PT 706513 T	31-10-2002
			RU 2137754 C1	20-09-1999
			SI 706513 T1	31-10-2002
			SK 161795 A3	03-07-1996
			US 5712298 A	27-01-1998
WO 0132165	A	10-05-2001	AU 1344501 A	14-05-2001
			BG 106623 A	28-02-2003
			BR 0015039 A	25-06-2002
			CA 2389293 A1	10-05-2001
			CN 1387433 T	25-12-2002
			CZ 20021443 A3	15-01-2003
			EP 1225884 A1	31-07-2002
			HU 0203682 A2	28-04-2003
			JP 2003513038 T	08-04-2003
			NO 20021937 A	30-05-2002
			SK 7292002 A3	03-12-2002
			TR 200201150 T2	23-09-2002
			WO 0132165 A1	10-05-2001
WO 0238155	A	16-05-2002	AU 2712302 A	21-05-2002
			CA 2427814 A1	16-05-2002
			US 2002055520 A1	09-05-2002
			WO 0238155 A1	16-05-2002
WO 0018388	A	06-04-2000	AU 1310300 A	17-04-2000
			BR 9914109 A	12-06-2001
			CA 2342603 A1	06-04-2000
			EP 1117402 A2	25-07-2001
			JP 2002525319 T	13-08-2002
			WO 0018388 A2	06-04-2000
			US 6509327 B1	21-01-2003
			US 6395746 B1	28-05-2002
			US 2002022629 A1	21-02-2002
US 4753945	A	28-06-1988	DE 3769812 D1	13-06-1991
			EP 0234854 A2	02-09-1987
			JP 2068611 C	10-07-1996
			JP 7088311 B	27-09-1995
			JP 62246524 A	27-10-1987

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/05524

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4753945 A		US 4956348 A	11-09-1990
US 5011843 A	30-04-1991	US 4975428 A	04-12-1990
		CA 1327525 C	08-03-1994
		EP 0345028 A2	06-12-1989
		JP 2025421 A	26-01-1990
US 6174878 B1	16-01-2001	AU 7062400 A	26-03-2001
		WO 0115678 A2	08-03-2001